Clinical Policy Title: Chromosomal microarray analysis

Clinical Policy Number: 02.01.21

Effective Date: September 1, 2016
Initial Review Date: August 17, 2016
Most Recent Review Date: August 17, 2016
Next Review Date: August 2017

Related policies:

CP# 02.01.08 Familial polyposis gene testing
CP# 02.01.14 Gene expression profile testing for breast cancer
CP# 11.04.02 Genetic testing for autism spectrum disorders
CP# 02.01.02 Genetic testing for breast and ovarian cancer
CP# 02.01.07 Genetic testing for cystic fibrosis
CP# 00.01.03 Genetic testing for cytochrome p450 Polymorphisms (CYP2C19)
CP# 05.01.03 Genetic testing for G1691A Polymorphisms Factor V Leiden
CP# 04.01.02 Genetic testing for Long QT syndrome (LQTS)
CP# 02.01.04 Genetic testing for primary autosomal recessive microcephaly
CP# 02.01.09 Genetic testing for rare diseases
CP# 13.01.01 Genetic testing for prostate cancer prognosis
CP# 09.01.09 Genetic testing in neurology
CP# 02.01.18 Genetic testing in sensorineural hearing loss
CP# 05.01.04 Molecular analysis for targeted therapy of non-small cell lung cancer
CP# 05.01.05 Molecular targeted therapy
CP# 02.01.03 Array comparative genomic hybridization testing

ABOUT THIS POLICY: AmeriHealth Caritas Northeast has developed clinical policies to assist with making coverage determinations.
AmeriHealth Caritas Northeast’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas Northeast when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Northeast’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Northeast’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Northeast will update its clinical policies as necessary. AmeriHealth Caritas Northeast’s clinical policies are not guarantees of payment.
Coverage policy

AmeriHealth Caritas Northeast considers the use of once-per-lifetime chromosomal microarray analysis (CMA) for evaluation of intellectual or developmental delay to be clinically proven and, therefore, medically necessary when all of the following criteria are met:

- There is clinical evidence of:
  - Multiple congenital anomalies not specific to a well-delineated genetic syndrome, OR
  - Apparent non-syndromic developmental delay/intellectual disability, OR
  - Autism spectrum disorders (ASDs).
- There is a care-coordinating, multidisciplinary team available for genetic and behavioral counseling for a tiered evaluation, which includes (a.) a primary care physician, (b.) a geneticist (who is a physician or a licensed genetic counselor), (c.) behavioral health specialists, (d.) speech/language testing and (e.) developmental/neurologic assessment.
- Family desire for engagement with the integrated multidisciplinary team is documented in the clinical record.

Limitations:

AmeriHealth Caritas Northeast considers the use of CMA genetic testing for screening for intellectual or developmental delay to be investigational and, therefore, not medically necessary.

All other uses of CMA genetic testing, except as specifically identified in the “Related Policies” above, are considered to be investigational and, therefore, not medically necessary.

Alternative covered services:

In-network visits to primary care physicians, behavioral health specialists, genetic counselors, as well as routine laboratory and radiographic, including magnetic resonance imaging (MRI), evaluations.

Background

CMA is a diagnostic application suitable for identifying congenital anomalies under certain conditions (i.e., abnormal fetal ultrasound, advanced maternal age or positive maternal serum aneuploidy screening); and for evaluating individuals with unexplained developmental delay (DD), ASD or intellectual disability (intellectual developmental delay, mental retardation). The latter is sometimes referred to as "ID."

CMA is also known as cytogenomic microarray analysis and collectively describes two different laboratory techniques:

- Array-based comparative genomic hybridization (CGH).
- Single nucleotide polymorphism (SNP) arrays.
While conventional karyotyping detects large changes in the structure or number of whole chromosomes (e.g., translocations, aneuploidy), CMA identifies genomic copy number variations (CNVs). CNVs are chromosomal imbalances created as a result of the deletion and/or duplication of one or more sections of deoxyribonucleic acid (DNA). CMA does not detect balanced chromosome rearrangements in which there is no gain or loss of DNA (balanced inversions or balanced translocations). CGH detects CNVs for relatively large deletions or duplications (including whole chromosome duplications as in trisomy). SNP is distinguished from CGH in the specificity of its application. In SNP specific known DNA sequence variants are evaluated.

In the prenatal setting, CMA requires an invasive procedure to collect intact fetal cells (for example, amniocentesis or chorionic villous sampling).

**Searches**

AmeriHealth Caritas Northeast searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality Guideline Clearinghouse and evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on July 21, 2016, using the terms “chromosomal microarray analysis.” We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

A CNV is a section (or sections) of the genome repeated once or multiple times over the length of the deoxyribonucleic acid (DNA) strand. The number of repeats in the genome varies between individuals in the human population. The discovery that CNVs — which can at times encompass large regions of DNA — are more common in patients with DD, ASD and ID has been the driver for the molecular diagnostic approach to identify these and similar conditions.

Historically, cytogenetic analysis (karyotyping) was performed to directly visualize chromosomes for any rearrangements, including gains and losses. However, in the modern era chromosomal microarray (CMA) technology has replaced cytogenetic analysis as a molecular diagnostic tool. CMA has greater resolution and can detect CNVs across the entire genome in a single test. CMA, as used here, encompasses all types of array-based genomic copy number analyses, including array-based CGH and SNP arrays.
A comprehensive narrative review by Sun (2015) described first-tier diagnostic genetic tests for impairment of intellectual and developmental maturation. The authors described (but did not specifically recommend) a panoply of genetic tests including CMA. They posited that benefits of genetic testing include an improved sense of empowerment for patient families, refining treatment options, providing prognosis, preventing comorbidities, avoiding unnecessary diagnostic tests, providing recurrence-risk counseling, and improving access to needed support or services. However, there was a paucity of evidence directly linking genetic testing to changes in health outcomes.

Millichap (2014) wrote a recommended diagnostic approach to genetic testing for autism and other developmental deficits on behalf of the American Academy of Pediatrics (AAP):

CMA is designated as a first-line test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology. Fragile X testing remains an important first-line test. The importance of considering testing for inborn errors of metabolism in this population is supported by a recent systematic review of the literature and several case series recently published. The role of brain MRI remains important in certain patients. The use of whole-genome testing is gaining popularity.

The American College of Medical Genetics (ACMG) has developed practice guidelines for the diagnosis of genetic disease that aim to improve the life of the affected individual (Schaefer 2013). The authors emphasize the importance of a “tiered” approach to the diagnostic evaluation. A full three-generation family history and pedigree analysis is recommended to identify known genetic disease syndromes or associated conditions:

- 22q11.2 deletions including velocardiofacial (Shprintzen) syndrome.
- Angelman syndrome.
- CHARGE syndrome.
- de Lange syndrome.
- Fragile X syndrome.
- MED12 disorders (including Lujan-Fryns syndrome).
- Prader-Willi syndrome.
- PTEN-associated disorders (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome).
- Rett syndrome.
- Smith-Lemli-Opitz syndrome.
- Smith-Magenis syndrome.
- Sotos syndrome.
- Tuberous sclerosis.
- PTEN, phosphatase and tensin.

The ACMG recommends that, in the presence of any of these syndromic presentations that genetic testing is indicated to identify a specific genetic cause and other comorbid conditions which may benefit from treatment. According to ACMG such a strategy has improved the diagnostic yield of genetic testing for ASD from 6 — 12 percent to 30 — 40 percent. There are no published studies demonstrating clinical improvements in outcomes of children subjected to such testing; and unfortunately, there are no more
than anecdotal reports whereby early initiation of behavioral health interventions, speech therapy and educational assistance have improved the lives of individuals so-affected.

An increasing number of relatively inexpensive and rapid testing methods are changing the landscape in the genetic diagnosis of disease. Although this policy is specific in the justifications for usage of CMA, an emerging body of evidence points to the benefits of using CMA in combination with other methods of genetic testing as important adjuncts in the diagnosis of ID, DD and ASD.

Szego (2016) noted that whole exome sequencing (WES) and whole genome sequencing (WGS) are shown to increase the diagnostic yield when applied to patients suspected of having ASD. Exome sequencing is a technique for sequencing all the protein-coding genes in a genome (known as the exome). It consists of first selecting only the subset of DNA that encodes proteins (known as exons), and then sequencing that DNA using any high-throughput DNA sequencing technology. WGS incorporates the protein-encoding sections of the DNA plus those sections of the strand that are not directly involved with protein creation (e.g., regulatory genes within the strand).

The authors emphasize that WES and WGS do not obviate the use of CMA. Microarray testing itself is a high yield test identifying an etiology in about 10 percent of cases of ID and DD (i.e., ASD). Together WES and CMA in tandem may identify the cause of ASD in 20 percent of cases. As such, genome-wide testing has now joined CMA as a part of the standard diagnostic assessment for patients with ID and DD.

Tammimies (2015) reported on 258 unrelated children with ID and DD recruited between 2008 and 2013 in Newfoundland and Labrador, Canada. The index individuals were stratified into 3 groups of increasing morphological severity: essential, equivocal, and complex (scores of 0-3, 4-5, and ≥6). All underwent CMA, with WES performed for 95 proband-parent trios. Overall 24 (9.3 percent, 95 percent CI, 6.1 — 13.5 percent) received a molecular diagnosis from CMA and 8 of 95 (8.4 percent, 95 percent CI, 3.7 — 15.9 percent) from WES. The yields were statistically different between the morphological groups.

Among the children who underwent both CMA and WES testing, the estimated proportion with an identifiable genetic etiology was 15.8 percent (95 percent CI, 9.1 — 24.7 percent; 15/95 children). This included 2 children who received molecular diagnoses from both tests. The combined yield was significantly higher in the complex group when compared with the essential group (pairwise comparison, p = .002). The authors concluded that the molecular diagnostic yields of CMA and WES were comparable, and the combined molecular diagnostic yield was higher in children with more complex morphological phenotypes in comparison with the children in the essential category.

**Summary of clinical evidence:**

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<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tr>
<th>Source</th>
<th>Title</th>
<th>Key points</th>
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| Szego (2016) | Whole Genome Sequencing as a Genetic Test for Autism Spectrum Disorder: From Bench to Bedside and then Back Again | - Narrative review noted that an increasing number of relatively inexpensive and rapid testing methods are changing the landscape in the genetic diagnosis of ASD.  
- WES and WGS increase the diagnostic yield when applied to patients suspected of having ASD.  
- CMA identifies an etiology of ASD in about 10 percent of cases.  
- Together WES and CMA may identify the cause of ASD in 20% of cases.  
- WGS and WES have now joined CMA as a part of the standard diagnostic assessment for patients with ASD. |
| Siu (2016) | Screening for Autism Spectrum Disorder in Young Children: US Preventive Services Task Force Recommendation Statement. | - Policy statement with regard to screening children aged 18 to 30 months for ASD:  
  "The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for ASD in young children for whom no concerns of ASD have been raised by their parents or a clinician." |
| AAP (2016) | AAP Statement on U.S. Preventive Services Task Force Final Recommendation Statement on Autism Screening | - Policy statement with regard to the USPSTF recommendations:  
  "The AAP stands behind its recommendation that all children be screened for ASD at ages 18 and 24 months, along with regular developmental surveillance. This recommendation is encapsulated in the Bright Futures Guidelines for Health Supervision of Infants, Children, and Adolescents, which serves as the blueprint for well-child visits and coverage under the Affordable Care Act. Health insurance coverage of ASD screening should not be impacted by the USPSTF statement." |
| AAFP (2016) | Autism Spectrum: Children (Aged 18 to 30 Months) | - Clinical preventive service recommendation:  
  "The AAFP concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for ASD in young children for whom no concerns of ASD have been raised by their parents or a clinician." |
| **Tammimies (2015)**
Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with Autism Spectrum Disorder | **Key points:**
- Prospective study of 258 consecutive children with ASD between 2008 and 2013 in Newfoundland and Labrador, Canada.
- All probands underwent CMA, with WES performed for 95 proband-parent trios.
- Of 258 probands, 24 (9.3%, 95%CI, 6.1% to 13.5%) received a molecular diagnosis from CMA
- Eight of 95 (8.4%, 95%CI, 3.7% to 15.9%) received a molecular diagnosis from WES.
- The yields were statistically different between the morphological groups. Among the children who underwent both CMA and WES testing, the estimated proportion with an identifiable genetic etiology was 15.8% (95%CI, 9.1% to 24.7%; 15/95 children).
- The combined yield was significantly higher in the complex group when compared with the essential group (pairwise comparison, P = .002).
| **Sun (2015)**
Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder | **Key points:**
- Technology assessment reviewed evidence for genetic testing in ASD.
- By test type, microarray testing is diagnostic on average in 7.8%, G-banded karyotyping is abnormal in at least 4%, and subtelomeric fluorescence in situ hybridization is positive in 3.5%.
- Testing for X-linked DD genes has a yield of up to 42% in males with an appropriate family history.
| **Millichap (2014)**
AAP Genetics Diagnostic Approach to Intellectual Disability or Global Developmental Delay. | **Key points:**
- "Chromosome microarray is designated as a first-line test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology."
- "The use of whole-exome sequencing as a diagnostic test is gaining popularity."
| **Geretsegger (2014)**
Music therapy for people with autism spectrum disorder | **Key points:**
- Music therapy for patients with ASD Review of 10 studies with 165 participants.
- Music therapy may also help enhance nonverbal communication skills within the therapy context.
- Music therapy may contribute to increasing social adaptation skills in children with ASD.
- The application of music therapy requires specialized academic and clinical training.
| **Schaefer (2013)**
Clinical Genetic Aspects of ASD Spectrum Disorders | **Key points:**
- All patients with ASDs should have a formal audiogram to rule out a significant hearing loss.
- Role of the patient-centered medical home.
- Referral for clinical genetics evaluation.
- Tiered evaluation.
- Genetic counseling.
- Treatment and follow up. |
Glossary

Autism spectrum disorders (ASD) — A collection of associated developmental disorders that affect the parts of the brain that control social interaction, verbal and non-verbal communication.

Chromosomal microarray analysis (CMA) — A diagnostic application suitable for evaluating individuals with unexplained developmental delay (DD), autism spectrum disease (ASD) or intellectual disability (intellectual developmental delay, mental retardation). It specifically looks for extra (duplicated) or missing (deleted) chromosomal segments, sometimes called copy number variants.

Copy number variant (CNV) — A phenomenon in which a section (or sections) of the genome is repeated once or multiple times over the length of the DNA strand. The number of repeats in the genome varies between individuals in the human population.

Fragile X syndrome — A genetic condition that causes a range of developmental problems, including learning disabilities and cognitive impairment. Males are usually more severely affected by this disorder than females.

Karyotype — The number of chromosomes in a cell; 23 pairs in normal humans. Abnormalities are associated with Down, Turner and Klinefelter syndromes.

Whole exome/genome sequencing (WES, WGS) — A technique for sequencing all the expressed genes in a genome (known as the exome). It is becoming a standard diagnostic tool for evaluating individuals with unexplained developmental delay (DD), autism spectrum disease (ASD) or intellectual disability (intellectual developmental delay, mental retardation).

References

Professional society guidelines/others:


Peer-reviewed references:


Moeschler J, Shevell M. Clinical Genetic Evaluation of the Child With Mental Retardation or Developmental Delays. Pediatr. 2006:117(6); 2304 – 2316


**Clinical trials:**

Searched clinicaltrials.gov on July 21, 2016 using terms “autism” and “disorder” | Open Studies. 144 studies found, 2 relevant.


**CMS National Coverage Determinations (NCDs):**

No NCDs were found at this time.

**Local Coverage Determinations (LCDs):**

No LCDs were found at this time.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

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<td>Cytogenic constitutional (genome-wide microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)</td>
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